NEUROtransmitter

Communicating our message.

Upcoming Events

CBTF 5k Walk/Run
October 9, 2016

Meadowbrook Park/
Candy Cane City
Chevy Chase, MD

**Registration information available on our website in August 2016.*

CBTF Casino Gala
November 5, 2016

Manor Club
New Carrollton Road
Rockville, MD
**Visit our website for more details.*

Raising Funds for Research

Funds raised will benefit pediatric bran tumor research and other CBTF programs

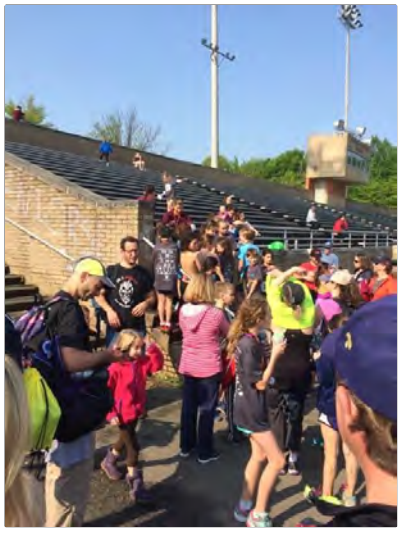
Be AMYazing

Best of Reston, Best of CBTF! AMYazing, Thank You!

Written by Carol Cornman, Vice President, CBTF

I am writing this based on inspiration and gratitude to Amy's Amigos.

Amy's Amigos was founded in 2008 and quickly grew to a large group of 12-year olds who offered friendship and support for classmate, Amy Boyle, who was battling brain cancer. After Amy's death from DIPG, inspired by her spirit, athleticism, and love of life, Amy's Amigos held the first Reston triathlon for kids in May of 2011.



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17th International Symposium on Pediatric Neuro-Oncology

Liverpool Convention Centre, 12th – 15th June 2016

Impact of New Molecular Understandings on Brain Tumor Clinical Trial Design and Performance

Feature Article

The Childhood Brain Tumor Foundation was pleased to be a Silver Sponsor for the comprehensive International Symposium on Pediatric Neuro-Oncology. Our *Neurotransmitter* Fall-Winter edition will include topics from the other conference days.

This summary covers a topic from Family Day and Educational Day, held June 11, 2016, related to molecular studies and clinical trials. The presentations were given by Dr. Roger J. Packer, Senior Vice-President, Neuroscience and Behavioral Medicine, Children's National Health System.

The new biologic understandings of childhood brain tumors have led to the development of an exciting array of potentially more effective therapies. However, to clinically best incorporate these therapies into patient care and evaluate the potential benefits of such therapies, clinical trial designs for patients must change. This includes trials done by national organizations

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The Childhood Brain Tumor Foundation

Our mission is to support and fund basic science or clinical research for childhood brain tumors. We are dedicated to heightening public awareness of this devastating disease.

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If you are interested in learning more about the Childhood Brain Tumor Foundation, Inc., please contact:

E-MAIL: cbtf@childhoodbraintumor.org or jeanneyoung@childhoodbraintumor.org
(E-mail preferred due to high volume of robo-calls)
TELEPHONE: 877-217-4166 or 301-515-2900

Volunteers welcome !

Impact of New Molecular Understandings on Brain Tumor Clinical Trial Design and Performance *(continued from page 1)*

such as Children's Oncology Group (COG) and the Pediatric Brain Tumor Consortium (PBTC), as well as more limited institutional studies and clinical trials supported by industry.

In the past, clinical trials have essentially been broken into three major subtypes, as described below. The subtypes remain, but trials need to get smarter and shorter to answer important questions in the care of children with brain tumors in a world that is rapidly changing.

General Principles of Clinical Trial Design

Phase I clinical trials are primarily designed to determine the maximum tolerated dose of a drug. For molecular targeted therapies, where toxicities may be less severe than standard chemotherapeutics, the maximum tolerated dose may not be reached and instead the trial is modified to determine the optimal dose to saturate the molecular target that can be safely given. Although phase I clinical trials are less likely than other stage trials to show clinical benefit for patients, they may result in tumor control, especially if the agent used is a molecular agent and the patient harbors a tumor which has a genetic aberration that is targeted by that molecular agent. Phase I trials are done in groups of three patients to assess toxicity at each drug dose, although another form of these trials is to use a rolling six design. A limitation of these trials is often availability, as the trials must be temporarily halted until each level of testing is completed.

Phase II clinical trials are performed to determine the efficacy of the agent chosen. Trials with molecularly-targeted agent are more effective when the patients chosen for the trial are pre-screened for having the molecular abnormality thought to be targeted by the drug being utilized. Biomarkers are often built into phase II clinical trials. For these trials, improved outcome measures are needed, such as assessment of functional outcomes, rather than just relying on radiographic outcomes.

Phase III are the goal standard and are randomized trials where the novel therapy is assessed against the best available therapy. Phase III trials are usually of longer duration, possibly for 5-10 years. Just as in phase II trials, better outcome measures are needed, especially functional outcome measures.

All of these trials need to be modified somewhat to better assess efficacy in the molecular era. Because molecular targeted therapy will only work in specific subsets of patients with tumors having the appropriate biologic makeup, such trials are highly dependent on selecting the right study population, the so called "enriched study population". Most trials are designed only to assess radiographic outcomes. Functional outcomes are often not included and functional outcomes can be more difficult to assess. Also there is reluctance by sponsoring agencies to fund the assessment of the needed functional outcomes, as they may significantly increase cost of the overall study.

To try to better conceptualize these issues, Dr. Packer addressed three tumor types and the impact biology is having on how trials are developed for those tumor types.

Challenges for Medulloblastoma

Medulloblastoma is the most common pediatric malignant brain tumor. One of

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Impact of New Molecular Understandings on Brain Tumor Clinical

(cont. from pg. 2)

the primary challenges for medulloblastoma is that medulloblastoma is not one tumor, but it is really multiple different tumors (at least biologically) lumped under the same name. Survival rates have been shown for patients with medulloblastoma to be as high as 90% at five years, the majority of 5-year survivors being cured of their disease. Although survival has improved, patients may suffer long-term sequel.

It is no longer rational to put all patients with medulloblastoma on a trial treating patients in the same way, as subgroups of patients with medulloblastoma have varying genetically-driven prognoses. For example, the WNT subgroup, most commonly found in older children, has the best survival and trials need to be designed that actually reduce therapy for those patients. A second major subset of patients with medulloblastoma, those with the Sonic-Hedgehog signature, are treated differently dependent on whether they have what is known as an "upstream" or "downstream" mutation in the Sonic-Hedgehog pathway. Therapy has to be tailored to those groups differently. As example, infants with one variety of Sonic-Hedgehog driven medulloblastomas are probably best treated with chemotherapy alone.

There still needs to be a consensus reached in how to best identify these molecular subtypes in those with medulloblastoma. Molecular testing is not available at many sites and it may take time to obtain molecular results, risking delays in treatment. Also, studies in patients with medulloblastoma, especially phase III studies, have to be shorter in duration, as the science moves quickly.

Challenges for Low-Grade Glioma (LLG)

The understanding of LGGs is in rapid transition. Many questions exist: including whether BRAF-fusion pi tumors are the only true type of pilocytic astrocytoma and whether non-BRAF fusion tumors, even though, at times, having histological features consistent with pilocytic tumors, should be considered a different tumor type. For LGGs it is unclear what is the best outcome measure is. Should response be based on neuroradiographic features alone or should it be based on functional improvement? It is known that in some children with LGGs may have radiographic improvement,

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Be AMYazing

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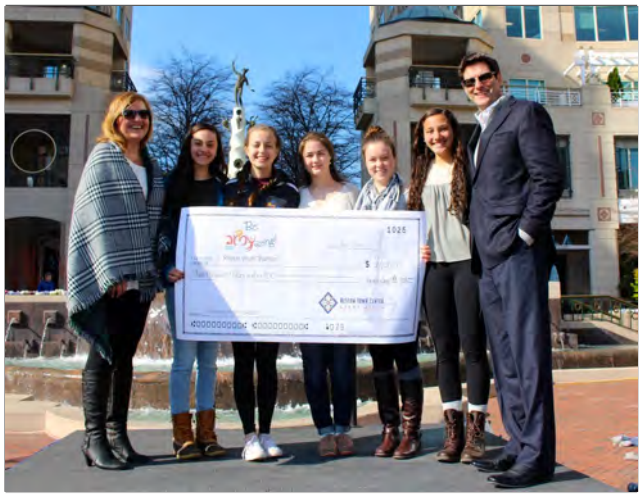
Amy's Amigos is a group of high school students who manage the event alongside many adult volunteers. In its first four years, the triathlon has raised over $63,000 for the Childhood Brain Tumor Foundation (CBTF) brain tumors.

In May of 2016 AMY's AMIGOS was the proud recipient of the BEST OF RESTON 2016 Vade Bolton-Anne Rodriguez Legacy Award. Kacey Hirshfeld, Olivia Wolfe and Hannah Becker accepted this award as the founders and race directors of the AMYazing triathlon held in memory of their friend Amy. Special recognition should also be given to the Amigos moms who lead up this event beside their beautiful daughters.



AMYazing is held yearly on Mother's Day at South Lakes High School in Reston, VA. Hannah, Mike Boyle and family always serve as additional event support to inspire Amy's legacy.

Children stride across that finish line with faces of will and determination in helping to make a difference in the fight for other children's lives. What a picture to remember and experience. I have been fortunate to experience this heartfelt, well organized, family event and it is wonderful. ♢

Photos from the 2016 AMYazing event on page 4.

In Honor of

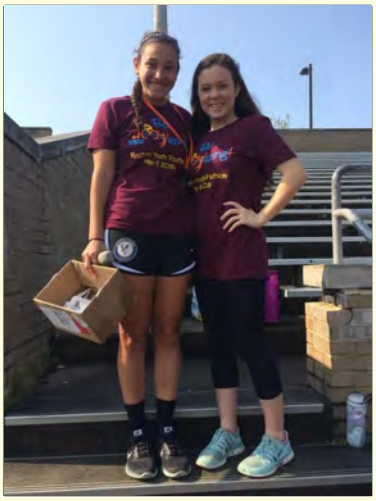
Alicia Gonzalez
Shannen Jones
Jeff Kahan

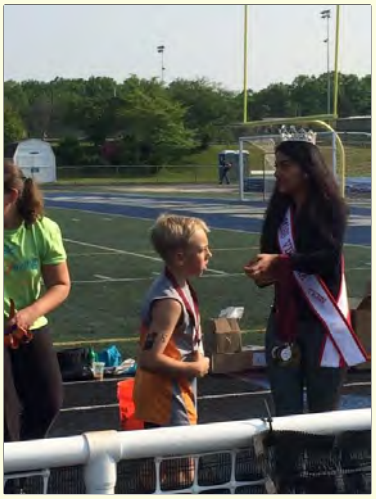
Stephen Schoenfeld
Adam Sinclair-Thompson
Camden Wiseman

Be AMYazing

(*photos continued from page 3*)

THANK YOU AMY'S AMIGOS, PARENTS, VOLUNTEERS AND ESPECIALLY PARTICIPANTS WHO HELP MAKE AMYAZING SO AMAZING EVERY YEAR!





RAPID AUTOPSY PROGRAMS AT CNHS, NCI, AND JOHNS HOPKINS

HELP FIND NEW TREATMENTS FOR DIPG

Diffuse Intrinsic Pontine Glioma (DIPG) is usually diagnosed in children between 4-10 yrs of age, and accounts for about 10-15 percent of all pediatric brain tumors. The cancer is invasive and infiltrates itself among healthy cells in the brainstem, making surgical removal impossible. Patients receive radiation to treat their symptoms, but most live only six months to two years after their diagnosis.

Because the cancer is located in the brainstem, the part of the brain that controls breathing and heart rate, the tumor is rarely biopsied, and for a long time scientists had no living cell lines with which to test treatments.

About five years ago families began to ask what they could do to help learn more about DIPG. Some families began giving permission for their children to undergo "rapid autopsies," which removed tumor tissue following the children's deaths. Researchers at Children's National Health System (Dr. Javad Nazarian), Johns Hopkins (Dr. Eric Raabe) and the National Cancer Institute (Dr. Katherine Warren) formed the Mid-Atlantic DIPG Consortium (MADC) to share resources and collaborate on DIPG research in hopes of learning as much as possible from each child's tumor. The goal of the MADC is to bring new treatments to patients with this dreaded tumor. All of the institutions have the capability of performing rapid autopsies, though CNHS has performed the most.

The generosity of these families has helped MADC researchers make key discoveries of DIPG biology. Dr. Warren and her co-investigators at NCI performed one of the first analyses of DNA changes in DIPG and found several targets that the MADC is now pursuing clinically. Dr. Nazarian and colleagues at CNHS identified protein and RNA fingerprinting of DIPG tumors using autopsy specimens. Their recent published work at *Nature Communications* described tumor evolution and partner driver mutations across tumor. Dr. Raabe was able to grow one of the first and most robust DIPG cell lines, giving researchers an opportunity to explore the molecular makeup of DIPG and to grow DIPG-like tumors in mice. This cell line, called JHH DIPG1, was one of the key cell lines used in a recent publication in the journal *Nature Medicine*, where researchers found that the FDA-approved drug panobinostat killed DIPG cells and shrank DIPG tumors in mice. A phase 1 clinical trial to test the drug's safety in children is now underway, thanks to the promising results of the *Nature Medicine* study. The MADC is continuing to build on its early successes, and the MADC is currently doing pre-clinical studies to find additional active drugs as well as drugs that may work with panobinostat.

The MADC researchers would like to thank all of the families for their generosity and their consideration of the next generation of patients with DIPG in donating tissue from these autopsies. *Drs. Nazarian, Raabe and Warren have all received CBTF funding for their work and wish to thank the supporters of CBTF for their support of pediatric brain tumor research.*

For more information:

CNHS Rapid autopsy program, contact:
Javad Nazarian, Ph.D.
202-476-6022,
email: jnazarian@cnmc.org
Madhuri Kambhampati, MS
202-476-5198,
email: mkambham-pati@childrensnational.org

NCI, contact:
Kathy Warren, M.D.,
301-325-9019,
email warren@mail.nih.gov or
Dr. Martha Quezado,
email quezadom@mail.nih.gov

Johns Hopkins Rapid Autopsy program:, contact:
Dr. Jody Hooper (pathologist)
410-955-3765, jhooper9@jhmi.edu
http://pathology.jhu.edu/RapidAutopsy/faqs.cfm

(continued from page 3)

Challenges for Diffuse Intrinsic Pontine Gliomas (DIPGs)

Over the past 50 years, despite multiple different attempts at altering therapy, no improvement has been seen in the outcome of children with DIPGs. Until recently the biology of these tumors has been poorly understood, primarily because tissue was not available for analysis. Newer protocols are requiring biopsy, in attempts to couple the new molecular understandings of these tumors to novel therapies.

In addition, DIPGs are just one type of diffuse infiltrating lesions that occurs in the brain. It is likely that infiltrating glial tumors, which involve the thalamus or the entire brain (gliomatosis cerebri), are biologically similar lesions and should be treated as a DIPG, if they have the same molecular signature.

There is an overall consensus that tissue removed by stereotactic biopsy is needed, not only for research purposes, but also for management. Autopsy tissue is also another very important type of tissue resource and this requires difficult discussions with the family, usually prior to the child's death. Molecular agents are nearly ready for treatment of childhood DIPGs and these agents must be rapidly incorporated into clinical trials.

To do all of these trials efficaciously, partnerships and trust between the physicians, the patients and their families are mandatory. Also there has to be a close working relationship with government agencies to allow these trials to move ahead more quickly and with industry to provide the needed drugs. The future of childhood brain tumor therapy is based on more exact molecular profiling of these tumors and using this information to determine what type of treatment is best for the child.

The Childhood Brain Tumor Foundation thanks Dr. Packer for reviewing and adding to the contents of this summary.

FUNDING

The Childhood Brain Tumor Foundation is looking forward to opening our 2017 grant process to researchers this fall.

The 2016 funded grants will be announced in the fall-winter newsletter with summaries about each research program and progress on previous funded grants.

Thank you to our supporters, sponsors, 5K teams, event attendees, and groups that raise funds for us through special events every year for supporting our mission. It is your support that allows us to offer research funding and educational materials.

Thank you from CBTF

to Individuals and Groups for holding special events and to the

Thank you

Ben Bellavia and Family-Booster T-shirt initiative

Nancy Bittle

Clarksburg Dance Marathon—In Memory of Sam Moore

FD Associates, Inc.

Rocky Hill Middle School In Memory of Sam Moore

Run with the Saints, In Memory of Lauren Lockard – Houston, TX

Recent Events

May 2016

Reston Youth League Be AMYazing

Rocky Hill Middle School Fundraiser

June 2016

International Symposium on Pediatric Neuro-Oncology, Liverpool, ENGLAND (CBTF is one of the sponsors)

HELPFUL RESOURCE LINKS

Thoughts Can Fuel Some Deadly Brain Cancers (paper in *Cell*), Michelle Monje "The discovery of a link between tumor growth and brain activity "has opened up a window into potential therapeutic interventions," says Batchelor
http://www.npr.org/blogs/health/2015/04/23/401723235/thoughts-can-fuel-some-deadly-brain-cancers

New technique treats brain tumors without life altering consequences, Maureen McFadden
http://www.wndu.com/home/headlines/New-technique-treats-brain-tumors-without-life-altering-complications-288854281

Targeted treatment produces rapid shrinkage of recurrent, BRAF mutant brain tumor, (craniopharyngioma), Massachusetts General
http://www.eurekalert.org/pub_releases/2015-11/mgh-ttp110615.php

Gracious Giving

Thank you to our friends who donated through workplace charitable giving campaigns this year, inclusive of the CFC, Maryland Charity Champaign and other independent campaigns.

Proud participant in the Combined Federal Campaign

The Childhood Brain Tumor Foundation, friends and families are very appreciative of your support.

Combined Federal Campaign / Children's Medical Charities of America (National) **12035**

Maryland Charities

Children's Medical & Research Charities of America

Campaign donations may be made for the United Way (**UW**) through the "donor option" or "donor choice."

Please check with your employer in reference to **UW** campaigns.

Thank you donors!

The Childhood Brain Tumor Foundation participates in the **Combined Federal Campaign (CFC) and Maryland Charities.**
Check our Website in the late summer or fall for our confirmed designated numbers. Check your campaign pamphlet for our **United Way number or write us in.**

22 Years of Excellence

It is through your support we
continue to fund programs and research
of excellence,
Thank you to all of our supporters, near and far!

Give Online

Visit our secure ***Give Online*** button on our Website: **www.childhoodbraintumor.org** (Discover, MC, VISA, and AE):

The Childhood Brain Tumor Foundation is dedicated to funding research for all pediatric brain tumor types.
Contact us if you have any questions:
cbtf@childhoodbraintumor.org

CBTF also accepts registration payments for the annual gala online. Be sure to include in the message box (number of tickets, names for ticket holders, and any additional donation). Tickets will be sent to the donor, unless noted as a donation in support of the event toward research.

Stock Donations

If you would like to make a stock donation, contact us:
cbtf@childhoodbraintumor.org

Our treasurer will provide you with the necessary details to proceed with your donation.
Thank you.

Powered By v-Dac Vehicle Donations

Vehicle Donation Program

CBTF accepts vehicle donations. Help make a difference, donate online or call 877-999-8322 and designate the Childhood Brain Tumor Foundation as your charity of choice. The service is totally free and includes convenient pick-up of your car, truck, or RV anywhere in the U.S.

QUICK FACTS FOR DONATING: You are eligible for an itemized TAX DEDUCTION. Find out details by checking the Foundation Web site: ***http://www.childhoodbraintumor.org***

Gift Matching Opportunities

Many companies offer a matching gifts program to support charitable organizations.

Your human resources department can tell you if such a program exists at your company. Ask them about the form that can be sent to the Childhood Brain Tumor Foundation reporting a contribution (donation or event contribution). The form states that they will match your contribution.

We return the form to the employer with the proper acknowledgment and information required.

Bequests, Planned Giving, and Trusts

Through a trust, bequest, or planned giving you can contribute to furthering the future research and programs of the Childhood Brain Tumor Foundation, Inc.

By including the CBTF in your estate planning you can minimize your taxes.

Jill Adleman
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Ross Barash
Debbie Bell
Cameo Beauchesne
Franco Borello
Amy Boyle
Kelly Brosius
Kelley Christine Bula
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William Thomas Camut
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Shawn Edwards
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Jared Daniel Foreman
Doyle Garrett
Herman Glaser
Elizabeth Carolyn Hahn
Ian Lennon Hahn
Kenneth Hahn
Donald Hartman

Remembrances

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Kristen Kenzig
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The Childhood Brain Tumor Foundation, Inc.

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Germantown, Maryland 20876

Toll free: 877.217.4166
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Master Card, VISA, and American Express donations for CBTF are accepted through our secure **Give Online** button on our Web site: **www.childhoodbraintumor.org**

Information request: (Note bellow specific interests) or address change or addition
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Include your E-mail address and name/address: _____
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The Childhood Brain Tumor Foundation
20312 Watkins Meadow Drive
Germantown, MD 20876

Address change requested

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Their generous support is deeply appreciated.

This newsletter is a free publication of the Childhood Brain Tumor Foundation.
We are funded through contributions and sponsorships from individuals and corporations.
Please let us know if your address has changed.

We welcome any donations in the way of financial support, commentary or information for this newsletter, or volunteer services to help with our operations.

CBTF is a tax-exempt, not for profit foundation IRS 501(c)(3) whose mission is to raise money to improve prognosis and quality of life for children suffering from brain tumors. Every year the requests continue to grow,

we need your support.
Help children with brain tumors.

SAVE THE DATE

Fundraise, support:
Annual Superheroes 5K Walk/Run—Sunday October 9, 2016
Gala—Saturday, November 5, 2016
For more information: Visit www.childhoodbraintumor.org

Children's Medical & Research Charities of America